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SPATIAL HETEROGENEITY NOT HOMOGENEITY OF THE MAGNETIC FIELD DURING EXPOSURES TO COMPLEX FREQUENCY-MODULATED PATTERNS FACILITATES ANALGESIA [1]

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Summary.—24 young (4 mo.) and 24 old (8 mo.) male Wistar rats were exposed for 30 min. on two consecutive days to either a sham-field or to a frequency-modulated magnetic field applied through a pair of solenoids (spatially heterogeneous strength) or a Helmholtz coil (spatially homogeneous strength). The maximum field strength was about 2 microTesla. The rats exposed to the spatially heterogeneous magnetic field but not the homogeneous magnetic field exhibited strong analgesia to thermal stimuli applied to the footpads immediately after the treatment and 30 min. later. The effect accommodated 38% of the variance in the latency to respond to the thermal stimuli. These results suggest that the practice by many researchers in bioelectromagnetism to design coils to generate maximum spatial homogeneity of intensities within the exposure volume when applying complex weak magnetic fields may actually diminish any biological effects.

During the last 10 years we have found that between 20 and 30 min. of whole body exposures to weak (1 microTesla) complex magnetic fields results in elevations of nociceptive thresholds for electrical and thermal stimuli (Fleming, Persinger, & Koren, 1994; Dixon & Persinger, 2001). The analgesic effect was equivalent to about 4 mg/kg of morphine. The most effective stimuli have been frequency-modulated magnetic fields whose intricate wave structures were generated by computer and whose point durations were between 1 and 3 msec. The magnetic field-induced analgesia has been evident immediately after 30 min. of exposure to these fields and has persisted for at least 30 min. after the removal of the fields. Their analgesic potency has been demonstrated in land snails (Thomas, Kavaliers, Prato, & Ossenkopp, 1997).

Many researchers in bioelectromagnetic research insist upon designing application systems that ensure maximal homogeneity of the strength of the field within the exposure volume. Whereas homogeneity of the vector of the magnetic field throughout the exposure area may be important for imaging of tissue (Magnetic Resonance Imaging), this precision may actually attenuate biomagnetic effects (Persinger, in press). Sharp spatial gradients of intensity rather than more homogeneous distributions have been known for the last 40 years to be most effective when strong static magnetic fields are em-

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ployed (e.g., Barnothy, 1964). McKay, Persinger, and Koren (2000) recently reported that a complex magnetic field with an extremely heterogeneous spatial gradient of intensity generated sequentially in each of the three spatial dimensions before it was presented simultaneously in all three dimensions produced powerful behavioral effects.

The present study was designed to discern if a complex magnetic field with the same temporal pattern produced more effective analgesia when its intensities were heterogeneous within the volume of exposure rather than homogeneous within the volume of exposure. We selected a frequency-modulated pattern as the temporal configuration of the applied magnetic field to produce the analgesia because it has been shown to be effective for both thermal and electric current nociception.

METHOD

Subjects

Forty-eight male albino Wistar rats were obtained from Charles River Laboratories in Quebec; 24 of the rats were 4 mo. of age while the other 24 rats were 8 mo. of age.

Apparatus

There were two exposure systems. The first apparatus, employed in previous studies (Fleming, *et al.*, 1994; Ryczko & Persinger, 2002) was a 25-cm × 25-cm × 25-cm plastic chamber within which the subjects were exposed to the field. Two large nails wrapped with wire were apposed to opposite sides of a plastic chamber, approximately 4.5 cm above the surface of the floor that was covered with ¼-in. corn cob bedding. The plane of the two poles of the solenoids was approximately the level of the head of an adult rat when walking on the bedding of the cage. The solenoids were connected so that the field was generated between the two nails ("poles"). The second apparatus was a 41-cm by 30.5-cm by 31-cm Helmholtz coil (30 ohms). The subjects were placed within a plastic container whose dimensions were 21 cm (length) by 28 cm (width) by 27.5 cm (height). The floor of this chamber also contained ¼-in. corncob for bedding.

The magnetic fields applied through both apparatus were a frequency-modulated pattern (previously described as "the Thomas Pulse"). The pattern was generated by converting a row of 849 numbers between 0 and 255 into voltages. Values above 127 were positive polarity while values below 127 were negative polarity. These voltages were converted by a custom-constructed digital-to-analogue device to the electric current that generated the magnetic field. The value for each point was presented for 3 msec. so that 2.55 sec. was required for the completion of each pattern. The time between generations of the pattern was 3 msec. Consequently the interstimulus (interpattern) interval was equivalent to the point duration. Stated alternatively, the presentation was continuous.

A Metex N380 meter coupled to a magnetic sensor (Electric Field Measurements, Rt. 183 W., Stockbridge, MA 01266) was employed to map the intensity of the field every 2 cm throughout the volume of each exposure area. For the spatially heterogeneous field the average strength within a radius of 2 cm from each pole (solenoid) was 2.4 microT (21 mG). At radii of 4 cm, 6 cm, 8 cm, and 10 cm from each pole the field strengths were 1.7 μT, 1.0 μT, and .5 μT, and .3 μT, respectively. Along the edges of the cage the values ranged between .15 and .35 microT. For the spatially homogeneous field the strength through the exposure volume for every 2 cm of space ranged between 2.4 μT and 3.0 μT. Within the vertical axis, the mean intensities for each of the six planes separated by 2 cm were .9, 1.0, .5, .4, .2, and .1 μT for the heterogeneous field and 2.3, 2.5, 2.9, 2.7, 3.0, and 2.3 μT for the homogeneous field. The overall coefficient of variation for all measurements, calculated by dividing the mean for all measurements by the standard deviation for all measurements was 23% for the heterogeneous field and 21% for the homogeneous field.

Procedure

The rats were housed in groups of three within standard wire cages for about three weeks after their receipt. *Purina* rat food and water were available *ad libitum*. The temperature was controlled between 19° and 20°C. The light dark cycle was 12:12 with local day beginning at 0800 hr.

When the experiment began rats were randomly assigned to one of four groups: spatially heterogeneous magnetic field, heterogeneous sham field, spatially homogeneous magnetic field, and homogeneous sham field. All rats were removed from their home cages and first tested on an Omnitech hotplate (56°C) for their nociceptive threshold. It was defined as the time between placement on the surface of the hotplate and when the rat lifted and licked either foot twice or when 60 sec. had elapsed. After criterion was achieved, the rat was removed immediately from the hotplate.

Equal numbers of rats from both age groups were randomly assigned to one of the four conditions. For the two field conditions (solenoids vs Helmholtz coil) the frequency-modulated field was presented for 30 min. Rats assigned to the sham-field groups were placed in the same chambers when all of the equipment was operating. The only difference between the field and sham-condition was the disconnection of the line from the computer during the latter. Background field strength from the equipment was between 10 nT to 20 nT. An exposure of 30 min. was employed because this duration was shown to be effective in previous studies (Fleming, *et al.*, 1994) and because it was within the range for practical clinical treatments (Baker-Price & Persinger, 1996).

After 30 min. had elapsed all of the rats were tested again on the hotplate for latency to respond before they were returned to their home cages. When another 30 min. had elapsed the rats were tested for a third time for their response latencies on the hotplate. This process was repeated on the second day. No more than eight rats (two per condition) were tested on any given day. Consequently, the experiment was composed of six separate blocks.

Each rat's score was the time in seconds to display the criterion response (licking either hind foot twice or 60 sec.) 30 min. after exposure to the treatments and 60 min. after exposure to the treatments had begun, subtracted from its baseline values. These net differences were employed as measurements because they have been more reliable indicators of response latency and accommodate individual differences in baseline measures. The primary experimental design was a four-way analysis of variance with two within-subject levels (day, time after treatment) and two between-subject factors (homogeneous vs heterogeneous field; sham-field vs field). All analyses involved SPSS software on a Vax computer.

Results

The results of the four-way analysis of variance showed a statistically significant difference in overall response latency (average of the values 30 min. and 60 min. after the beginning of the treatment for both days) for rats exposed to the different apparatus ($F_{1,44} = 7.22$, $p = .01$; eta-squared = .14). The rats exposed to the frequency-modulated magnetic field displayed significantly greater latencies, suggestive of greater analgesia, compared to the rats exposed to the sham-field ($F_{1,44} = 25.00$, $p < .001$; eta-squared = .36). However, there was a statistically significant interaction between type of apparatus and the presence or absence of the magnetic field ($F_{1,44} = 17.19$, $p < .001$; eta-squared = .38).

Post hoc Tukey analysis ($p < .05$) showed that the primary source of the interaction was the longer response latencies for the rats that had been exposed to the spatially heterogeneous magnetic field compared to all other groups that did not differ significantly from each other. The means and standard errors of the means for the four groups for the net differences in response latencies between the baseline and 30 min. and 60 min. after the beginning of the treatments are shown in Fig. 1.

The differences between days and the interaction between days and apparatus, type of field and days, and type of field, apparatus, and days (all *df*s = 1,44) were not statistically significant (all *F*s < 1.25, $p > .05$). Similarly, there were no significant differences between trials (30 min. vs 60 min.) and these interactions or interactions between trials and days (all *df*s = 1,44). A subsequent 5-way analysis of variance with an additional between-subject

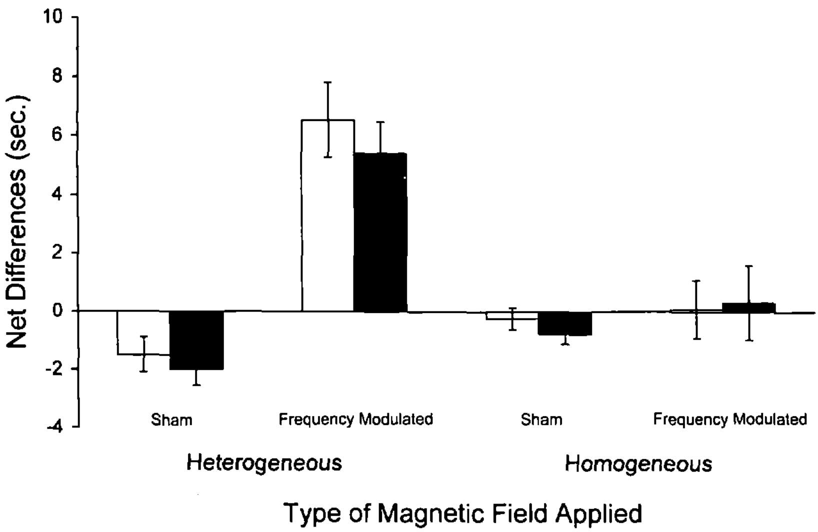

FIG. 1. Net difference in seconds between baseline responses to a nociceptive stimulus (hot plate) and the response to this stimulus 30 min. and 60 min. after exposure to sham fields or a frequency-modulated magnetic field the intensities of which were heterogeneous (.1 microT to 2.0 microT) or homogeneous (2 microT) over the exposure volume.

factor (young vs old rats), again showed a significant interaction between type of apparatus and type of field ($F_{1,40}=21.44$, $p<.001$; 35% of variance explained). There was also a statistically significant interaction ($F_{1,40}=7.41$, $p<.01$; eta-squared = .15) among age of the rats, the presence of the field, and the type of apparatus. *Post hoc* Tukey analysis ($p<.05$) showed that the primary source of this interaction was due to the longer latencies for both days and for both trials per day for the older rats ($M=9$ sec.) exposed to the heterogeneous field compared to the younger rats ($M=4$ sec.), whereas the other six groups did not differ significantly from each other.

Discussion

The results of this study confirm the reports of Ryczko and Persinger (2002) and Dixon and Persinger (2001) that 30 min. exposures to frequency-modulated magnetic fields increase the analgesic response to nociceptive thermal stimulation. These fields were created by computer transformation of a row of numerical values between 0 and 255. They were converted by a digital-to-analogue converter to voltage and then to current within a pair of solenoids or a Helmholtz coil. This same set of solenoids also facilitated analgesia for nociceptive stimulation of the foot pads by electric current (Fleming, *et al.*, 1994).

The absence of statistically significant interactions between days or trials and the presence of the magnetic fields indicates that the analgesic effect was consistent over both days and both trials. In the latter case, this means that the analgesia was still present 30 min. after removal from the field. That the increased latency to respond was due to a motor or muscular artifact rather than to analgesia is not likely. During several unpublished experiments the first author has found that, although magnetic field-exposed rats displayed the increased thermal latency compared to sham-field controls, they did not differ significantly from control rats with respect to ambulatory behavior. For example, the mean and standard deviation for the numbers of squares traversed in an open field for 15 rats 30 min. after they had been exposed to the frequency-modulated field were 10.9 and 3.7. These values for another 15 rats 30 min. after they had been exposed to the sham-field were 13.6 and 9.9, respectively.

The interaction between age and treatment with the heterogeneous magnetic field was related to the marked increased analgesia displayed by the older rats. The proclivity for older rats, particularly those over 1 yr. of age, to show marked enhancement of analgesia to complex magnetic fields compared to younger rats, has been observed in several unpublished experiments involving about 100 rats. Persinger (1987) had suggested that older organisms, including human beings, may become more sensitive to ambient electromagnetic fields and to various types of therapies employing complex magnetic fields. The metabolic model is that lower rates associated with aging allow the contribution of the magnetic fields to be amplified over the energetic background. The mathematical model is the structure represented by the applied magnetic fields transiently compensate for the entropy that defines senescence. We assume the stability of emergent properties arising from the complex chemistry of ontogeny might be affected by the organism's cumulative history of exposure to the dynamic components of the earth's magnetic field.

Because both application geometries displayed similar values for the coefficient of variation, which was calculated by dividing the mean of the values for each horizontal plane in vertical space by the standard deviation for these values, relative variability through space may not be a critical factor for production of the magnetic field-induced analgesia. These values were comparable because the standard deviation and the mean for the heterogeneous field were .57 and .12 μT and 2.7 and 0.5 μT for the homogeneous field. These results suggest that the absolute gradient may be more important than the relative gradient.

The results of this experiment also support our hypothesis that complex magnetic fields with spatially heterogeneous intensities would be more effective in producing analgesia than the same complex magnetic fields with more homogeneous gradients of intensity within the exposure volume (Persinger, in press). We reasoned that the greater the heterogeneity of the intensity of magnetic pattern with a complex temporal structure within the space occupied by the organism, the more likely microspatial patterns can be represented within the organism. We have imagined these patterns exist as a temporal stream of magnetic "cells" or domains whose specific characteristics change every 3 msec. (the point duration of the numbers that compose the field). These changes in spatial configurations of the field within these "cells" would be analogous to the changing spatial arrangements within a rotating kaleidoscope.

The movements might be similar to the scroll-shaped waves that rotate around a curved filament in three-dimensional space during Belousov-Zhabotinsky reactions (Keener & Tyson, 1988). The filaments around which the scroll rotates are not stationary but move through space until a stable configuration is achieved or it disappears. These scroll rings shrink in size and collapse in finite time. While present they might contain information relevant to the population of cells immersed within the scroll.

Consequently a rat, either stationary or moving through the spatially heterogeneous magnetic field, would have several tens of these domains represented within the same organ system, particularly the larger ones such as the adipose tissue, brain, liver, or muscle at any given 3-msec. interval. The reader may note we have carefully employed the term "represented" rather than "induced." Induction implies the direct transformation between the applied magnetic field and the induction of an electric field, accommodation for the reluctance of the tissue, and the formation of electrical currents within interstitial fluids. We do not think the mechanism involves the induction of electric current determined by change in the field strength per unit time (Faraday's Law). However, we cannot exclude the possibility that a higher spatial gradient of the field, as the rat ambulated through it, could have induced more electric current than moving through a homogeneous field.

We can also not exclude at this time the possibility that the analgesic effect may be related to intensities less than 2 microTesla. Although the major difference between the two apparatus was the spatial gradients of the strengths of the applied field within the exposure area, the heterogeneous exposure area was on average about one-fifth (.5 microT) the intensity of the homogeneous field (2.5 microT). In addition, there may be some as yet undetected difference between magnetic fields generated through and between iron cylinders (nails) that represent actual magnetic poles and magnetic fields induced perpendicular to coils of wire.

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